201-14995

HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN FOR

2-OXETANONE, 4-METHYLENE

"DIKETENE"

CAS NO.: 674-82-8

PREPARED BY:
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DIKETENE DERIVATIVES TASK FORCE

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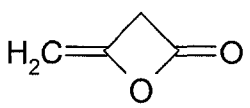
OVERVIEW

The Diketene Derivatives Task Force (DDTF) of the Color Pigments Manufacturers Association (CPMA) and its member companies hereby submit for review and public comment the test plan for 2-oxetanone, 4-methylene (diketene; CAS No.: 674-82-8) under the U. S. Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of the DDTF and its member companies to use either existing data on diketene or data that will be generated in the future under the ICCA HPV program, predictive computer models, or data from structurally similar compounds to adequately fulfill the Screening Information Data Set (SIDS) for physical-chemical properties, environmental fate, ecotoxicity, and toxicological and human health effects. The DDTF believes that these data, in total, will fulfill all the requirements of the US HPV program without need for the conduct of any additional tests by the DDTF.

TEST PLAN SUMMARY

CAS No. 674-82-8 	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	Y	-	N	Y	N
Partition Coefficient	Y	-	-	Y	N	Y	N
Water Solubility	Y	-	Y	-	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y	-	Y	-	N	Y	N
Biodegradation	Y	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	N	Y	-	N	N	N
Acute Toxicity to Aquatic Invertebrates	N	-	-	-	-	N	N
Toxicity to Aquatic Plants	N	-	-	-	-	N	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	N	Y	-	N	Y	N
Repeated Dose Toxicity[1]	N	-	-	-	-	-	N
Genetic Toxicity – Mutation[1]	N	-	-	-	-	-	N
Genetic Toxicity – Chromosomal Aberrations[1]	N	-	-	-	-	-	N
Developmental Toxicity[1]	N	-	-	-	-	-	N
Toxicity to Reproduction[1]	N	-	-	-	-	-	N

1. Endpoint is completed through the use of data from the chemical surrogates' ethyl acetoacetate and methyl acetoacetate.

TEST PLAN FOR DIKETENE

I. Background

Diketene is a clear colorless liquid of very high purity. Diketene is used as a chemical intermediate in the production of acetoacetate esters and acetoacetanilides, dyes, color pigments, pharmaceuticals, food preservatives and insecticides. It is a very chemically unstable substance that rapidly degrades upon contact with water to form acetoacetic acid (diacetic acid). Diacetic acid is capable of undergoing further decomposition or can be metabolized in mammalian systems to form acetone and CO_2, diketene also readily reacts with oxidizing materials and is capable of undergoing extremely dangerous polymerization reactions if not properly handled. It is manufactured and transported in closed-systems and sold to a limited number of customers who also handle this material in closed systems. There is no known direct or consumer use of the chemical where exposure to the general population may occur. Exposure to diketene by employees is minimized by its manufacture, transport, and use in closed-systems as well as the use of good industrial hygiene practices. Exposure is also self-limited by the fact that this chemical is known to be extremely irritating to the eyes and mucous membranes of the respiratory tract. Exposure to the environment is unlikely except under conditions of an accidental release during manufacture or transport.

It is also important to point out that this chemical has been sponsored by Wacker-Chemie GmbH as part of the ICCA HPV initiative (See ICCA HPV website). Accordingly, as part of that program SIDS dossier and a SIDS screening information assessment report (SIAR) and a SIDS initial assessment profile (SIAP) will be prepared that will cover the same endpoints of concern required in the US EPA's HPV program. As such, the DDTF does not want to initiate any testing that may be duplicative of test that may have already been completed by Wacker-Chemie GmbH to fulfill its obligation under the ICCA program.

II. Justification for the Use of Data from Surrogate Chemicals

As a means to reduce the number of tests that may be conducted, the EPA allows for the use of categories to group together chemicals that are structurally similar to characterize specific SIDS endpoints (USEPA 1999a). At this time the only data that exist to assess toxicity in mammalian systems is acute toxicity data. Accordingly, the DDTF believes that the endpoints assessing genotoxicity, repeated exposure toxicity and developmental and reproductive toxicity hazards can be evaluated through the use of structural surrogates.

As noted above, diketene is an extremely unstable molecule that is well known to rapidly degrade upon contact with water to form acetoacetic acid (AAA; CAS No.: 541-50-4). AAA is a compound that is endogenously produced in the body as part of normal metabolism of lipids where it undergoes further decomposition to form acetone and CO_2. In addition, the compounds ethyl acetoacetate (EAA; CAS No.: 141-97-9) and methyl acetoacetate (MAA; CAS No.: 105-45-3) which are compounds formed by ester linkages between AAA and the respective alcohols, ethanol and methanol, are also fully anticipated to be metabolized by esterase activity in biological systems to yield AAA and the respective alcohols. EAA is in the ICCA HPV program and was recently reviewed at SIAM 12 where it was concluded to be a chemical of low risks to both the environment and to human health. This was based on a robust set of data covering all SIDS endpoints (See OECD website for published SIAP). The complete data set for this compound should be available to the public through the EPA. MAA is in the US EPA HPV program and, similar to EAA, has a complete SIDS database available to the public.

Thus, it is the conclusion of the DDTF that due to the rapid degradation and or metabolism of diketene to AAA upon contact with water and based on the strong assumption that the metabolism of MAA and EAA will also yield AAA (actual metabolism data for EAA and MAA are not available) the hazard assessment of diketene for all end points beyond acute exposure can be deduced from the information available on MAA and EAA.

III. Description of the Test Plan for Each SIDS Endpoint

A. Physical –Chemical Data

Melting point –	Values for this endpoint were obtained from reputable textbooks.
Boiling point -	Values for this endpoint were obtained from reputable textbooks.
Vapor pressure -	Values for this endpoint were obtained from reputable textbooks.
Partition coefficient -	A value for this endpoint was obtained using KOWIN (v1.67), a computer estimation program (1).
Water solubility -	Values for this endpoint were obtained from a reputable textbook and using WSKOW (v1.41), a computer estimation program(1)
Conclusion:	All endpoints are satisfied by, either actual data found within reputable textbooks or from acceptable estimation models. These data are of sufficient quality to conclude that no additional testing is required.

B. Environmental Fate Endpoints

Photodegradation -	A value for this endpoint was obtained using AOPWIN (v1.91), a computer estimation program (1).
Stability in Water -	A value for this endpoint was obtained from two studies. The first was a measure of the kinetic heat of reaction of hydrolysis showing the reaction to be exothermic. The second study involved the automatic recording titration, which was used to determine the hydrolysis rate constant.
Biodegradation -	This endpoint was satisfied through the use of existing data from a multi-day ready biodegradability assessment using a Modified MITI Test (I) OECD TG-301C.
Transport between Environ. Compartments (Fugacity) -	Transport between environmental compartments was determined using EPIWIN:EQC, a Level III Fugacity computer modeling system(1).
Conclusion:	All endpoints have been satisfied using data or estimation models that are of sufficient quality to conclude that no additional testing is necessary. The principle use of this substance is a chemical intermediate and because the substance is manufactured and handled in closed-systems it is highly unlikely to enter into the environment.

C. Ecotoxicity Data

Acute Toxicity to Fish -	This endpoint contains data from a single acute toxicity study in Golden Orfe. However, the reliability of this study is of questionable validity. A prediction of the acute toxicity of AAA using the ECOSAR estimation program within EPIWIN indicates the material to be of very low toxicity potential.

Acute Toxicity to Aquatic Invertebrates - No data are available for this end point. A prediction of the acute toxicity of AAA using the ECOSAR estimation program within EPIWIN indicates the material to be of very low toxicity potential.

Toxicity to Aquatic Plants - No data are available for this end point. A prediction of the acute toxicity of AAA using the ECOSAR estimation program within EPIWIN indicates the material to be of very low toxicity potential.

Conclusion: Diketene is a highly reactive, unstable chemical substance. In presence of water it rapidly hydrolyzes to produce AAA. The AAA further decomposes to acetone and carbon dioxide. The principle use of this substance is a chemical intermediate and because the substance is manufactured and handled in closed-systems it is highly unlikely to enter into the environment. The testing of diketene in aquatic environments would be of questionable value due to its inherent instability. However, since the results of ECOSAR estimation programs indicate the diketene degradation product AAA to be of such low toxicity and due to the fact that Wacker-Chemie GmbH has accepted the ICCA HPV Initiative to prepare a SIDS Dossier for diketene, the DDTF does not want to initiate any testing that may be duplicative of test that may have already been completed by Wacker-Chemie GmbH to fulfill its obligation under the ICCA program that are not available to the DDTF.

C. Toxicity Data

Acute Toxicity - This endpoint was fulfilled by data from several studies following oral, dermal, and inhalation exposure. All studies were conducted prior to establishment of the OECD Test Guidelines and GLP testing requirements. They are nevertheless of sufficient quality to conclude that no new testing is needed.

Repeated Dose Toxicity - No data on diketene are available for this end point. Thus, this endpoint was fulfilled by data from the chemical surrogates MAA and EAA. In addition, data from three carcinogenicity studies conducted under National Cancer Institute sponsorship and guidelines have been briefly summarized.

Genetic Toxicity Mutation - No data on diketene are available for this end point. The purpose of these *in vitro* studies is as a predictor for *in vivo* carcinogenicity. Based upon the absence of such an effect in the three carcinogenicity studies it would appear that such data would be of limited value. In addition, data from the chemical surrogates MAA and EAA can be utilized to complete this endpoint.

Genetic Toxicity Chromosomal Aberration - No data on diketene are available for this end point. The purpose of these *in vitro* studies is as a predictor for *in vivo* carcinogenicity. Based upon the absence of such an effect in the three carcinogenicity studies it would appear that such data would be of limited value. In addition, data from the chemical surrogates MAA and EAA can be utilized to complete this endpoint.

Developmental Toxicity - No data on diketene are available for this end point. Thus, this endpoint was fulfilled by data from the chemical surrogates MAA and EAA. In addition, the rapid hydrolysis rate and chemical reactivity of diketene in

aqueous environments would result in its decomposition to AAA before it reached the placental membrane or the conceptus.

Reproductive Toxicity - No data on diketene are available for this end point. Thus, this endpoint was fulfilled by data from the chemical surrogates MAA and EAA. In addition, the rapid hydrolysis rate and chemical reactivity of diketene in aqueous environments would result in its decomposition to AAA before it reaches reproductive organs.

Conclusion: Diketene is a highly reactive, unstable chemical substance that presents very real hazards if improperly handled making the shipping and testing of this molecule extremely difficult. In presence of water it rapidly hydrolyzes to produce AAA which is known to be metabolized to acetone and carbon dioxide. The principle use of this substance is a chemical intermediate and because the substance is manufactured and handled in closed-systems exposure to humans is unlikely. Since complete SIDS datasets have been developed on MAA and EAA which are strongly believed to be metabolized to AAA, the DDTF believe no further toxicity testing of diketene are believed to be warranted. Furthermore, no additional testing is proposed, as Wacker-Chemie GmbH has accepted the ICCA HPV initiative to prepare a SIDS dossier for diketene and the DDTF does not want to conduct any tests which may be duplicative.

IV. Evaluation of Data for Quality and Acceptability

The collected data were reviewed for quality and acceptability following the general US EPA guidance (3) and the systematic approach described by Klimisch *et al.* (4). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicity and human health endpoints per US EPA recommendations (3). The codification described by Klimisch *et al.* (4) specifies four categories of reliability for describing data adequacy.

These are:

(1) Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) assurances or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or were insufficiently documented.

(4) Not assignable: Includes studies or data in which insufficient detail to assign a rating, *e.g.*, listed in abstracts or secondary literature.

References

1. EPI™ Suite. Version 3.11. U.S. Environmental Protection Agency, Washington, DC 20460.

2. US EPA. 1999a. The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

3. USEPA, 1999b, Determining the Adequacy of Existing of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/1999.

4. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol. 25:*1-5.